PATENT CLAIMS:

1. A purified polynucleotide selected from the group consisting of

   i) a polynucleotide comprising nucleotides 1 to 5376 of SEQ ID NO:1, corresponding to the coding sequence of PAPP-A2, as deposited with DSMZ under accession number DSM 13783; and

   ii) a polynucleotide encoding a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and

   iii) a polynucleotide encoding a fragment of a polypeptide encoded by polynucleotides (i) or (ii), wherein said fragment

      a) has a proteolytic activity specific for Insulin Like Growth Factor Binding Protein 5 (IGFBP-5), or a derivative thereof, or any other substrate; and/or

      b) is recognised by an antibody, or a binding fragment thereof, which is capable of recognising a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and/or

      c) competes with a polypeptide having the amino acid sequence as shown in SEQ ID NO:2 for binding to a cell surface receptor having an affinity for said polypeptide; and

   iv) a polynucleotide, the complementary strand of which hybridizes, under stringent conditions, with a polynucleotide as defined in any of (i), (ii) and (iii), said polynucleotide encoding a polypeptide having the amino acid sequence as shown in SEQ ID NO:2, or a fragment thereof, wherein said fragment

      a) has a proteolytic activity specific at least for Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); and/or

b) is recognised by an antibody, or a binding fragment thereof, which is capable of recognising a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and/or

c) competes with a polypeptide having the amino acid sequence as shown in SEQ ID NO:2 for binding to a cell surface receptor having an affinity for said polypeptide; and

v) a polynucleotide comprising a nucleotide sequence which is degenerate to the nucleotide sequence of a polynucleotide as defined in any of (iii) and (iv),

and the complementary strand of such a polynucleotide.

2. A purified polynucleotide according to claim 1 and comprising the coding sequence as shown in SEQ ID NO:1.

3. A polynucleotide according to claim 1 and encoding a polypeptide the amino acid sequence as shown in SEQ ID NO:2.

4. A polynucleotide according to claim 1 and encoding a fragment of the polypeptide having the amino acid sequence as shown in SEQ ID NO:2, wherein said fragment

a) has a proteolytic activity specific at least for Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); and/or

b) is recognised by an antibody, or a binding fragment thereof, which is capable of recognising a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and/or

c) competes with a polypeptide having the amino acid sequence as shown in SEQ ID NO:2 for binding to a cell surface receptor having an affinity for said polypeptide

5. A polynucleotid according to claim 1, wherein the complementary strand of said polynucleotide hybridizes, under stringent conditions, with a polynucleotide according to any of claims 2 to 4.

6. A polynucleotide according to claim 1 and comprising a nucleotide sequence which is degenerate to the nucleotide sequence of a polynucleotide according to any of claims 3 and 4.

7. A polynucleotide according to claim 1, said polynucleotide comprising the complementary strand of a polynucleotide according to any of claims 2 to 6.

8. A polynucleotide according to any of the preceding claims operably linked to a further polynucleotide comprising nucleic acid residues 5377 to 8527 of SEQ ID NO:1, corresponding to a 3' untranslated region, or a fragment thereof, or SEQ ID NO:1.

9. A recombinant DNA molecule in the form of an expression vector comprising an expression signal operably linked to a polynucleotide according to any of claims 1 to 7.

10. A host organism transfected or transformed with the polynucleotide according to any of claims 1 to 8, or the vector according to claim 9.

11. Host organism according to claim 10, wherein said organism is a mammalian organism.

12. An isolated polypeptide comprising or essentially consisting of the amino acid sequence of SEQ ID NO:2, or a fragment thereof, wherein said fragment

i) has a proteolytic activity specific at least for Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); and/or

ii) is recognised by an antibody, or a binding fragment thereof, which is capable of recognising a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and/or

iii) competes with a polypeptide having the amino acid sequence as shown in SEQ ID NO:2 for binding to a cell surface receptor with an affinity for said polypeptide.

13. Polypeptide according to claim 12, wherein the fragment comprises or essentially consists of amino acid residues 234 to 1791 corresponding to the mature part of PAPP-A2, including any processing variant thereof.

14. Polypeptide according to claim 12, wherein the fragment comprises or essentially consists of amino acid residues 1 to 233 corresponding to the prepro part of PAPP-A2.

15. Polypeptide according to claim 12, wherein the fragment comprises or essentially consists of amino acid residues 23 to 233 corresponding to the pro part of PAPP-A2.

16. Polypeptide according to claim 12, wherein the fragment comprises or essentially consists of amino acid residues 1 to 22 corresponding to the signal peptide or leader sequence of PAPP-A2.

17. Polypeptide according to any of claims 14 to 16 operably linked to the mature part of PAPP-A2 corresponding to amino acid residues 234 to 1791 of SEQ ID NO:2.

18. Polypeptide according to any of claims 12 to 17, wherein said polypeptide is a recombinant polypeptide.

19. Polypeptide according to any of claims 12 to 18, wherein the polypeptide is free of human proteins, or other proteins natively associated with said polypeptide.

20. A composition comprising i) the polynucleotide according to any of claims 1 to 8, and/or ii) the vector according to claim 9, and/or iii) the host organism according to any of claims 10 and 11, and/or iv) the polypeptide according to any of claims 12 to 19, in combination with a physiologically acceptable carrier.

21. A pharmaceutical composition comprising i) the polynucleotide according to any of claims 1 to 8, and/or ii) the vector according to claim 9, and/or iii) the host organism according to any of claims 10 and 11, and/or iv) the polypeptide according to any of claims 12 to 19, in combination with a pharmaceutically acceptable carrier.

22. A method for producing an antibody with specificity for the polypeptide according to claim 12, said method comprising the steps of

i) providing a host organism,

ii) immunizing the host organism with the polypeptide according to claim 10, and

iii) obtaining said antibody.

23. An antibody having specific binding affinity for a polypeptide according to claim 12.

24. Antibody according to claim 23, wherein said antibody is selected from the group consisting of monoclonal antibodies and polyclonal antibodies.

25. Antibody according to claim 24, wherein said antibody is monoclonal.

26. A method for producing the polypeptide according to claim 18, said method comprising the steps of

i) providing a suitable host organism,

ii) transfecting or transforming the host organism provided in step i) with the polynucleotide according to any of claims 1 to 8, or the vector according to claim 9,

iii) culturing the host organism obtained in st p ii) under conditions suitable for expression of the polypeptide encoded by th polynucleotide or the vector; and optionally

iv) isolating from the host organism the polypeptide resulting from recombinant expression by the host organism.

27. The method of claim 26, wherein said host organism is a mammalian cell.

28. A method for inhibiting and/or reducing expression of PAPP-A2 in a cell by means of anti-sense technology, said method comprising the steps of

i) providing the polynucleotide according to claim 7,

ii) transfecting or transforming a cell capable of expressing PAPP-A2 with said polynucleotide provided in step i),

iii) culturing the cell obtained in step ii) under conditions suitable for hybridization of the polynucleotide provided in step i) to a complementary polynucleotide in said cell involved in the expression of PAPP-A2, and

iv) inhibiting and/or reducing the expression of PAPP-A2 in said cell.

29. Method of claim 28, wherein the antisense polynucleotide and the complementary polynucleotide are co-expressed from distinct polynucleotide molecules.

30. A method for detecting PAPP-A2, or measuring the level of PAPP-A2, in a biological sample obtained from an individual, said method comprising the steps of

i) obtaining a biological sample from said individual,

ii) detecting PAPP-A2 in said sample by detecting

a) a polypeptide according to claim 12; and/or

b) a polynucleotide in the form of mRNA originating from PAPP-A2 expression, and/or

c) PAPP-A2 specific protease activity, preferably by detecting cleavage of IGFBP-5, a derivative thereof, or any other suitable substrate for PAPP-A2.

31. Method of claim 30, said method comprising the further step of comparing the PAPP-A2 or the level of PAPP-A2 detected in step ii) with a predetermined value selected from the group consisting of

I) a predetermined amount and/or concentration of PAPP-A2; and/or

II) a predetermined amount and/or concentration of PAPP-A2 mRNA; and/or

III) a predetermined PAPP-A2 specific protease activity.

32. Method of claim 31, wherein said predetermined value is indicative of a normal physiological condition of said individual.

33. The method of claim 30, wherein said biological sample is selected from the group consisting of blood, urine, pleural fluid, oral washings, tissue biopsies, and follicular fluid.

34. The method of claim 30, wherein said level of PAPP-A2 is measured as PAPP-A2 specific protease activity.

35. The method of claim 30, wherein said level of PAPP-A2 is measured as amount of PAPP-A2 protein.

36. The method of claim 30, wherein said level of PAPP-A2 is measured as amount of PAPP-A2 messenger RNA.

37. The method of claim 35, wherein said amount of PAPP-A2 protein is measured by immunochemical analysis.

38. The method of claim 37, wherein said amount of PAPP-A2 protein is detected by at least one monoclonal antibody.

39. The method of claim 30, wherein said PAPP-A2 protein is detected in a complex comprising at least one additional component, preferably a polypeptide.

40. The method of claim 30, wherein said PAPP-A2 is detected as a PAPP-A2 monomer.

41. The method of claim 30, wherein said PAPP-A2 is detected as a PAPP-A2 dimer.

42. A method of diagnosing a clinical condition in an individual, said method comprising the steps of

i) performing the method of any of claims 30 to 41, and

ii) diagnosing the clinical condition.

43. Method of claim 42, wherein said clinical condition is a fetal abnormality.

44. The method of claim 43, wherein said fetal abnormality is selected from the group consisting of Trisomy 21, Trisomy 18, Trisomy 13, and Open Spina Bifida.

45. The method according to claim 43, wherein said fetal abnormality is ectopic pregnancy, open spina bifida, neural tube defects, ventral wall defects, Edwards Syndrome, Pateaus Syndrome, Turner Syndrome, Monosomy X or Kleinfelter's Syndrome.

46. The method of claim 43, wherein said clinical condition is an altered growth state selected from the group consisting of a growth promoting state and a growth inhibiting state.

47. The method of claim 46, wherein said clinical condition is selected from the group consisting of restenosis, atherosclerosis, wound healing, fibrosis, myocardial infarction, osteoporoses, rheumatoroid arthritis, multiple myeloma, or cancer.

48. A method for detecting expression of a polynucleotide according to claim 1 in a biological sample, said method comprising the steps of:

i) providing a biological sample putatively containing a polynucleotide according to claim 1, and

ii) contacting the biological sample with a polynucleotide comprising a strand that is i) complementary to the polynucleotide according to claim 1 and ii) capable of hybridizing thereto, and

iii) allowing hybridization to occur, and

iv) detecting the hybridization complex obtained in step iii),

wherein the presence of the hybridization complex is indicative of the expression in the biological sample of the polynucleotide according to claim 1, or a fragment thereof.

49. A method for identifying an agent inhibiting the protease activity of PAPP-A2, said method comprising the steps of

i) incubating a) the polypeptide according to claim 12 and b) a predetermined substrate for said polypeptide, and c) a putative inhibitory agent, and

ii) determinining if proteolysis of said substrate is inhibited.

50. The method of claim 49, wherein said substrate comprises a polypeptide.

51. The method of claim 50, wherein said substrate comprises an internally quenched fluorescent peptide.

52. The method of claim 50, wherein said substrate comprises or essentially consists of IGFBP-5, or a fragment thereof.

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53. An inhibitory agent obtainable according to any to the method of any of claims 49 to 52.

54. Use of the inhibitory agent according to claim 53 in the manufacture of a medicament for treating a clinical condition in an individual in need of such treatment.

55. A method for identifying an agent enhancing the protease activity of PAPP-A2, said method comprising the steps of

i) incubating a) the polypeptide according to claim 12 and b) a predetermined substrate for said polypeptide, and c) a putative enhancer agent, and

ii) determinining if proteolysis of said substrate is enhanced.

56. The method of claim 53, wherein said substrate comprises a polypeptide.

57. The method of claim 54, wherein said substrate comprises an internally quenched fluorescent peptide.

58. The method of claim 54, wherein said substrate comprises or essentially consists of IGFBP-5, or a fragment thereof.

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59. An enhancing agent obtainable according to any to the method of any of claims 54 to 57.

60. Use of the enhancing agent according to claim 59 in the manufacture of a medicament for treating a clinical condition in an individual in need of such treatment.

61. A method of treatment by therapy of an individual, said method comprising the step of administrating to said individual i) the pharmaceutical composition according to claim 21, and/or ii) the inhibitory agent according to claim 53, and/or the enhancing agent according to claim 59.

62. A method for purification of PAPP-A2 or complexes of PAPP-A2 with other proteins, said method comprising the steps of

i) provising a polyclonal or monoclonal antibody with specific binding affinity for a polypeptide according to claim 12,

ii) purifying PAPP-A2 by means of affinity chromatography.

63. A method of diagnosing a clinical condition or diagnosing predisposition to said clinical condition in an individual comprising the steps of

a) providing a body sample from said individual; and
b) measuring the level of a complex selected from the group consisting of PAPP-A/proMBP, PAPP-A2/proMBP, PAPP-A/PAPP-A2, PAPP-A/PAPP-A2/proMBP, proMBP/ANG and proMBP/ANG/C3dg in said body fluid sample; and
c) diagnosing the clinical condition or diagnosing predisposition to the clinical condition, wherein the level of the complex above or below a predetermined value is indicative of the clinical condition or predisposition to the clinical condition.

64. A method of diagnosing a clinical condition or diagnosing predisposition to said clinical condition in a mammalian fetus comprising the steps of

a) providing a body fluid sample from the mother of said fetus; and

b) measuring the level of a complex selected from the group consisting of PAPP-A/proMBP, PAPP-A2/proMBP, PAPP-A/PAPP-A2, PAPP-A/PAPP-A2/proMBP, proMBP/ANG and proMBP/ANG/C3dg in said body fluid sample; and

c) diagnosing the clinical condition or diagnosing predisposition to the clinical condition, wherein the level of the complex above or below a predetermined value is indicative of the clinical condition or predisposition to the clinical condition.

65. The method according to any of claims 63 and 64, wherein the clinical condition is selected from the group consisting of Down's syndrome, preeclampsia and acute coronary syndrome, including unstable angina and myocardial infarction.

66. The method according to any of claims 63 and 64, wherein the complex is PAPP-A/proMBP and the clinical condition is selected from the group consisting of Down's syndrome and acute coronary syndrome, including unstable angina and myocardial infarction.

67. The method according to any of claims 63 and 64, wherein the complex is proMBP/ANG and the clinical condition is Down's syndrome.